REMARKS

Claims 1–4, 6-12, and 18-25 are pending. Claims 1-4, 6-7, 9-12, 18-20, and 23-25 have been amended to read "μm" where the claims presently read "mm." Support for the amendments is found in the claims as originally filed. The amendments merely correct a typographical error that was introduced with the preliminary amendment filed March 20, 2002.

Claims 10-12, dependent on claim 9, were further amended to change the term "member" to "microsphere" for proper antecedent basis and clarity .

Claims 19 and 20 were further amended to depend from new claim 26, and thus provide proper antecedent basis to the term "well." Support for new claim 26 can be found throughout the specification, see e.g. page 10, line 37. No new matter was added.

For the Examiner's convenience, a copy of the "Pending Claims" is appended hereto (Appendix A) and a copy of the "Marked-up Version of the Claims" is also appended hereto (Appendix B).

Applicant thanks the Examiner for considering the references listed on the 1449 received June 11, 2001 in Paper No. 5 and October 15, 2001 in Paper No. 6. Additionally, Applicant thanks the Examiner for considering the International Search Report filed with Paper No. 6.

Priority

Applicant respectfully disagrees with the Examiner's assertion that the earlier-filed application does not provide support for claims of the current application. Particularly, Applicant believes that Provisional application 60/181,631 filed 10 February 2000 (hereinafter "'631"), upon which priority is claimed, provides support under 35 USC. §112 for claims 1-4, 6-12, 18-20, and 23-25 of the present application as follows:

The '631 application teaches a first and second subpopulation of microspheres on page 2, paragraph 5. Specifically, the application states that a number of different samples are loaded onto a slide. The different samples are then processed in parallel. In addition, the title of the application is "Alternative Substrates and Formats for Bead-Based Array of Arrays™." Beads and microspheres are synonymous with regard to this application, as is well known in the art. The disclosure of a number of different samples loaded onto a bead-based array correlates with multiple subpopulations of microspheres, and particularly the claim element of a first and second

subpopulation of microspheres. Item 6 of page 2 of the '631 application further enumerates measures that can be taken to separate individual arrays. Such disclosure presupposes the existence of subpopulations that make up the individual arrays. Clearly a first and second subpopulation of microspheres is supported by the '631 application. Curiously, in connection with a §103 rejection (discussed in detail below) the Examiner states that Demers teaches a first and second subpopulation and cites col. 6, lines 10-26 as support. Applicant asserts that the '631 application provides clear support for this claim limitation. By contrast, Applicant submits that the support for a first and second subpopulation found by the Examiner for the Demers art rejection is misplaced, as col. 6, lines 10-26 does not provide such disclosure.

The'631 application also provides support for a random distribution of microspheres on a substrate surface. Specifically, the application states that the present invention describes the use of alternative substrates for randomly-assembled Bead Arrays™ and Array of Arrays™. Moreover, the application states that preferred embodiments of the substrate may comprise a plastic or glass format of a microscope slide (page 1, number 4, second and third paragraphs). A randomly assembled array, in the context of this application, necessarily means that microspheres are randomly distributed on the surface of the substrate, because the arrays are "bead-based" (as the title indicates) and assembly requires distribution on the beads on the surface of the substrate.

In contrast to the Examiners position, Applicant submits that the '631 application also teaches a distance between centers of a first and second microsphere subpopulation. Specifically, on the bottom of page 1, the application states that for high resolution scanners (<5μm), close spacing (<15μm) between bead features can be employed to create extremely high density arrays. For more common lower resolution scanners (>5μm), bead spacing could be increased to 15-20μm. These statements combined with the discussion above regarding first and second microsphere subpopulations makes clear that the '631 application provides proper support for the claims of the present application. Spacing between centers of microspheres is a convenient point of reference for measurement purposes. Moreover, the distance can be computed by back-calculating the dimensions of a slide and dividing by the number of wells (2-4 million).

Claim Rejections under 35 USC §112, second paragraph

Claims 1-4 and 6-12 are rejected under 35 USC. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that claims 1-4 and 6-12 are indefinite for the recitation "is formatted to the dimensions of a microscope slide" because it is unclear whether the recitation is a method step of formatting the substrate.

Without agreeing with the Examiner's rejection, Applicant has amended claim 1, as suggested by the Examiner. For consistency, claim 18 has also been amended in the same manner as the amendment to claim 1. Support for amended claims 1 and 18 is found on page 9, lines 24-29. Therefore, Applicant submits that the amendments contain no new matter. Applicant respectfully requests entry of the amendments and withdrawal of the rejection.

Claim Rejections under 35 USC §103

Items 7, 9, and 11

The Examiner has rejected claims 1-4, 6-12, 18-20, and 23-25 under 35 USC. §103(a) as being unpatentable over Demers *et al.*, U.S. Patent No. 5,840,256 (hereinafter "Demers") in view of Van Ness *et al.*, U.S. Patent No. 6,248,521 (hereinafter "Van Ness") and Walt *et al.*, WO 98/40726 (hereinafter "Walt"). The Examiner further rejects these claims under 35 USC. §103(a) as being unpatentable over Walt in view of Noonan *et al.*, U.S. Patent No. 6,129,896 (hereinafter "Noonan") and Van Ness. The Examiner also rejects these claims under 35 USC. §103(a) as being unpatentable over Chee *et al.*, WO 00/39587 (hereinafter "Chee").

Demers teaches a plate for reaction systems. The plate has a plurality of uniformly sized reaction cells formed in its upper surface wherein the density of the reaction cells is at least about 10 wells per cm^2 (col. 1, lines 52-53). Demers states that the density of wells must be no more than about 350 per cm^2 (col. 1, line 66). Moreover, Demers does not teach a microscope slide.

Van Ness teaches methods and an apparatus for performing amplification and other enzymatic reactions on nucleic acid molecules that have been printed onto a solid substrate such as a silicon wafer or glass slide. Van Ness does not teach a random distribution of microspheres, nor a first and second subpopulation of microspheres.

Walt teaches a microsphere-based analytic chemistry system in which microspheres carrying different chemical functionalities may be mixed together while the ability is retained to

identify the functionality on each bead using an optically interrogatable encoding scheme. An optical fiber bundle sensor is also disclosed in which the separate microsphere may be optically coupled to discrete fibers or groups of fibers within the bundle. The functionalities are encoded on the separate microspheres using fluorescent dyes and then affixed to wells etched in the end of the bundle. Thus, a single sensor may carry thousands of chemistries on those microspheres exhibiting reactions and then may be decoded to identify the corresponding functionality.

Noonan teaches a biosensor chip and manufacturing method. The biosensor is manufactured by synthesizing a plurality of functional moieties onto a plurality of fibers, wherein each fiber receives one moiety. Once the functional moieties are synthesized onto the fibers, the fibers are bundled in a predetermined arrangement. The bundled fibers are then bonded together to fix their predetermined arrangement. Finally, the bonded fiber bundle is sliced into a plurality of individual devices, or chips.

Chee teaches a sensor composition comprising a composite array of individual arrays to allow for simultaneous processing of a number of samples, as well as methods of making and using the arrays.

In contrast, the present claims provide a microscope slide composition and a method for making such a composition . The microscope slide composition comprises a substrate with a surface comprising discrete sites, the sites separated by a distance of less than 50 μm, wherein the substrate comprises the dimensions of a microscope slide; and a population of microspheres comprising at least a first and a second subpopulation, wherein the first subpopulation comprises a first bioactive agent and the second subpopulation comprises a second bioactive agent and wherein the microspheres are randomly distributed on the surface.

Applicant notes that there are three requirements to establish a *prima facie* case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP § 2143).

Moreover, it has long been the rule that the claimed invention, as a whole, cannot be said to have been obvious absent some reason or motivation given in the prior art why someone would have been prompted to combine the teachings of the references. *In re Bond*, 15 USPQ2d

1566 (CAFC 1990). Furthermore, as the Federal Circuit indicated in *Dow Chemical Co. v. American Cyanamid Co.*, 2 USPQ2d 1350 (Fed. Cir. 1987), a rejection of obviousness cannot stand based on a reference of a proposed combination of references which leads one of ordinary skill in the art away from the claimed invention. In *Dow Chemical Co. v. American Cyanamid Co.*, 2 USPQ2d 1350 (CAFC 1987), the Federal Circuit affirmed a district court holding that various patents were not invalid as obvious over a prior art reference because the prior art reference "taught away" from the inventions in those patents. The Examiner is directed to *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990) where the Federal Circuit held that prior art which would "discourage" the ordinarily skilled artisan from attempting the claimed invention cannot validly support a rejection under 35 USC. § 103.

Applicant believes that the Examiner is attempting to employ a hindsight reconstruction of the present invention, piecing together the teachings of the various references by using the present application as a guide for doing so. As the Federal Circuit stated in *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992),

> "[I]t is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. . . .One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

First, Applicant apologizes for any confusion that may have resulted from the typographical errors that occurred in the "Response to Restriction Requirement and Preliminary Amendment," which was mailed on March 20, 2002. In particular, as such claim language is relevant to Demers, according to claim 1, the distance separating the discrete sites is "less than 50 μm" and not 50 mm.

There is no motivation to combine the references. Demers teaches away from the present invention as stated in Column 1, line 56-Column 2, line 3. Demers states "[p]referably, the density of cells is no more than about 350 per cm^2." Demers would not provide motivation to combine the references, because it would discourage one of ordinary skill in the art from attempting the claimed invention. Moreover, the examiner is using the present invention as a blueprint to piece together the teachings of the present invention. This is impermissible under *In re Fritch,* hence the rejections over Demers, Van Ness, and Walt are obviated.

Assuming *arguendo* that motivation to combine the references exists, not each and every element of the present invention is taught, because the distance between the discrete sites in Demers is orders of magnitude larger than the distance between the discrete sites in the present invention, and Van Ness, and Walt do not make up for the deficiencies of Demers. Specifically, the present invention claims that the sites are separated by a distance of less than 50 μm, whereas Demers teaches the pitch between reaction cells is at least 0.5 mm (col. 2, lines 2-6). The Demers patent teaches the spacing of wells far larger than that of the present invention and guides against too high a density. Therefore, Demers teaches away from the present invention. Where Demers is not cited as a prior art reference, Van Ness, Walt, and Noonan also do not teach each and every element of the claims. None of the prior art references teach sites are separated by a distance of less than 50 μm. Accordingly, Applicant submits that Demers, Van Ness, Walt, and Noonan alone or in combination fail to teach each element of claims 1-4, 6-12, 18-20, and 23-24. Applicant respectfully requests that the Examiner withdraw these rejections.

Items 8, 10 and 12

The Examiner has rejected claims 21 and 22 under 35 USC. §103(a) as being unpatentable over Demers, Van Ness, Walt, and Gentalen *et al,*. U.S. Patent No. 6,306,643 B1 (hereinafter "Gentalen"). Moreover, claims 21 and 22 are rejected under 35 USC. §103(a) as being unpatentable over Walt in view of Noonan and Gentalen. The Examiner further rejects claims 21 and 22 under 35 USC. §103(a) as being unpatentable over Chee in view of Demers, Van Ness, and Gentalen.

Chee, Demers, Van Ness, Walt, and Noonan have been summarized above.

Gentalen teaches arrays of polynucleotide probes having at least one pooled position. The array comprises a support having at least three discrete regions. The first region bears a pool of polynucleotide probes comprising first and second probes. The second region bears the first probe without the second probe and a third region bears the second probe without the first probe. In contrast, claims 21 and 22 teach the method of claim 18 wherein the ratio of the first and second subpopulations are at least 1:36 and 1:100, respectively.

Again, there are three requirements to establish a *prima facie* case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or

to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP § 2143).

In this case, the Examiner has essentially used impermissible hindsight to conclude that the combination of these references leads to the impetus "to provide subpopulations of nucleic acid microspheres in a ratio of 1:36 or 1:100 to detect the low copy number sequence without signal interference from the high copy number sequence." Nowhere in these references is there motivation to combine to arrive at the present invention. None of the references contains any motivation to take the teachings of a microscope slide composition comprising: a substrate with a surface comprising discrete sites, said sites separated by a distance of less than 50 μm, wherein said substrate comprises the dimensions of a microscope slide; and a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and said second subpopulation comprises a second bioactive agent wherein said microspheres are randomly distributed on said surface and wherein the ratio of said first and said second subpopulation of microspheres is at least 1: 36 or 1: 100 to achieve the present invention.

Even if some motivation to combine the references existed, not all the elements of independent claim 18 are met using the cited prior art references. Furthermore, Gentalen does not make up for the deficiencies of the independent claim, and therefore, the cited prior art references do not read on the present invention. Even assuming that all elements of independent claim 18 are present, the Gentalen reference still does not read on the elements of claims 21 and 22. The ratios of Gentalen refer to probe ratios. The ratios in claims 21 and 22 refer to ratios of microspheres. Furthermore the ratios of Gentalen are typically equimolar, or in some assays, some pools have "more of one probe than another" (col. 11, line 29-33). Claims 21 and 22 recite microsphere ratios of 36 or 100 times the amount of the first subpopulation to the second subpopulation, not merely more of one subpopulation than the other. Additionally, in Gentalen, certain regions of the support have no probes, whereas other regions have probes "in excess." This does not read on claims 21 and 22, because the ratios of microspheres in claims 21 and 22 refer to blank beads versus beads comprising bioactive agents. That is to say, the present invention states that the ratios are utilized for spacing and density purposes, whereas Gentalen states that ratios are used to demonstrate binding strengths of the different probes (col 11, lines

36-40). Gentalen does not teach the specific optimal ratios that are taught in the present experiment, or even "ratios" as someone of ordinary skill in the art would understand in this context. Column 11, lines 13-44 and claim 9 of Gentalen merely teach that certain regions of the support have no probes, whereas other regions have probes "in excess."

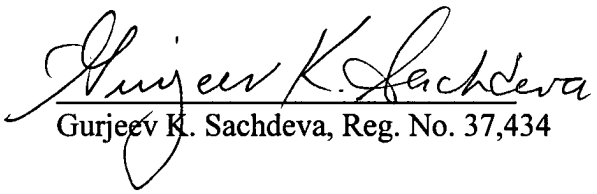
Accordingly, Applicant submits that claims 21 and 22 are not obvious in view of the cited references. Applicant therefore respectfully requests the Examiner withdraw these rejections.

CONCLUSION

Applicant submits that the claims are now in form for allowance. An early notification to that effect is respectfully requested.

Respectfully submitted,

DORSEY & WHITNEY LLP



Gurjeev K. Sachdeva, Reg. No. 37,434

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

1090358

Appendix A

Pending Claims

1. (Amended) A microscope slide composition comprising:

a) a substrate with a surface comprising discrete sites, said sites separated by a distance of less than 50 μm, wherein said substrate comprises the dimensions of a microscope slide; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and said second subpopulation comprises a second bioactive agent, wherein said microspheres are randomly distributed on said surface.

2. (Amended) A composition according to claim 1, wherein said sites are separated by a distance of less than 25 μm.

3. (Amended) A composition according to claim 1, wherein said sites are separated by a distance of less than 15 μm.

4. (Amended) A composition according to claim 1, 2 or 3, wherein said sites are separated by a distance of at least about 5 μm.

6. (Amended) The composition according to claim 1, wherein the distance between centers of a first and second microsphere of said first subpopulation is at least 5 μm.

7. (Amended) The composition according to claim 6, wherein the distance between said first and second microsphere of said first subpopulation is less than about 100 μm.

8. A composition according to claim 1, wherein said substrate further comprises first and second assay locations, wherein said first and second subpopulations are distributed in said first and second assay locations.

9. (Amended) A composition according to claim 8, wherein the distance between a first and second microsphere of said first subpopulation is less than about 100 μm.

10. (Amended) A composition according to claim 9, wherein the distance between a first and second microsphere of said first subpopulation is less than about 50 μm.

11. (Amended) A composition according to claim 9, wherein the distance between a first and second microsphere of said first subpopulation is less than about 15 μm.

12. (Amended) A composition according to claim 9, 10 or 11, wherein the distance between said first and second microsphere of said first subpopulation is at least about 5 μm.

18. (Amended) A method for making a microscope slide composition comprising:

a) providing a substrate with a surface comprising discrete sites, said sites separated by a distance of less than 50 μm, wherein said substrate comprises the dimensions of a microscope slide; and

b) randomly distributing population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and said second subpopulation comprises a second bioactive agent.

19. (Amended) The method according to claim 26, wherein said wells are separated by a distance of less than 25 μm.

20. (Amended) The method according to claim 26, wherein said wells are separated by a distance of less than 15 μm.

21. The method according to claim 18, wherein the ratio of said first and said second subpopulation is at least 1: 36.

22. The method according to claim 18, wherein the ratio of said first and said second subpopulation is at least 1: 100.

23. (Amended) The method according to claim 18, wherein the distance between the centers of a first and second microsphere of said first subpopulation is at least 5 μm.

24. (Amended) The method according to claim 18, wherein the distance between the centers of a first and second microsphere of said first subpopulation is at least 15 μm.

25. (Amended) The method according to claim 18, wherein the distance between a first and second microsphere of said first subpopulation is at least 50 μm.

26. (New) The method according to claim 18, wherein said discrete sites are wells.

Appendix B

Marked-up Version of the Claims

1. (Amended) A microscope slide composition comprising:

a) a substrate with a surface comprising discrete sites, said sites separated by a distance of less than 50 [mm] μm, wherein said substrate [is formatted to] comprises the dimensions of a microscope slide; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and said second subpopulation comprises a second bioactive agent, wherein said microspheres are randomly distributed on said surface.

2. (Amended) A composition according to claim 1, wherein said sites are separated by a distance of less than 25 [mm] μm.

3. (Amended) A composition according to claim 1, wherein said sites are separated by a distance of less than 15 [mm] μm.

4. (Amended) A composition according to claim 1, 2 or 3, wherein said sites are separated by a distance of at least about 5 [mm] μm.

6. (Amended) The composition according to claim 1, wherein the distance between centers of a first and second microsphere of said first subpopulation is at least 5 [mm] μm.

7. (Amended) The composition according to claim 6, wherein the distance between said first and second microsphere of said first subpopulation is less than about 100 [mm] μm.

8. A composition according to claim 1, wherein said substrate further comprises first and second assay locations, wherein said first and second subpopulations are distributed in said first and second assay locations.

9. (Amended) A composition according to claim 8, wherein the distance between a first and second microsphere of said first subpopulation is less than about 100 [mm] μm.

10. (Amended) A composition according to claim 9, wherein the distance between a first and second microsphere [member] of said first subpopulation is less than about 50 [mm] μm.

11. (Amended) A composition according to claim 9, wherein the distance between a first and second microsphere [member] of said first subpopulation is less than about 15 [mm] μm.

12. (Amended) A composition according to claim 9, 10 or 11, wherein the distance between said first and second microsphere [member] of said first subpopulation is at least about 5 [mm] μm.

18. (Amended) A method for making a microscope slide composition comprising:

a) providing a substrate with a surface comprising discrete sites, said sites separated by a distance of less than 50 [mm] μm, wherein said substrate [is formatted to] comprises the dimensions of a microscope slide; and

b) randomly distributing a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first [bioactve] bioactive agent and said second subpopulation comprises a second bioactive agent.

19. (Amended) The method according to claim [18] 26, wherein said wells are separated by a distance of less than 25 [mm] μm.

20. (Amended) The method according to claim [18] 26, wherein said wells are separated by a distance of less than 15 [mm] μm.

21. The method according to claim 18, wherein the ratio of said first and said second subpopulation is at least 1: 36.

22. The method according to claim 18, wherein the ratio of said first and said second subpopulation is at least 1: 100.

23. (Amended) The method according to claim 18, wherein the distance between the centers of a first and second microsphere of said first subpopulation is at least 5 [mm] μm.

24. (Amended) The method according to claim 18, wherein the distance between the centers of a first and second microsphere of said first subpopulation is at least 15 [mm] μm.

25. (Amended) The method according to claim 18, wherein the distance between a first and second microsphere of said first subpopulation is at least 50 [mm] μm.

26. (New) The method according to claim 18, wherein said discrete sites are wells.